Aus der Kinderklinik der Universität Bern

Leitung: Professor Dr. E. Glanzmann

BRONCHIAL ASTHMA IN CHILDREN AND ITS TREATMENT WITH NICOTINE AMIDE

INAUGURAL-DISSERTATION

zur Erlangung der Doktorwürde
der Medizinischen Fakultät
der Universität Bern

vorgelegt von

Julian Macow Yood

von New York, N.Y., USA

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DEFINITION

Asthma is dyspnea of a characteristic "wheezy" type caused by obstruction to the flow of air in and out of the lungs. Such wheezy breathing occurs in a variety of conditions, and may be either continuous or paroxysmal: hence the term asthma should be used to indicate, not a disease but a symptom. Bronchial asthma is a term formerly applied to the kind of asthma that occurs in attacks, in contradistinction to "cardiac asthma" or "renal asthma" in which the symptoms are more persistent. In this paper we are concerned with bronchial asthma.

HISTORY

Asthma (Gr. = pant) was described as early as about 400 B.C. by Hippocrates. He makes a certain distinction between different forms of pathological respiration. He mentions that asthma occurs in the years of childhood and youth, whereas dyspnea usually appears in advanced age. The Greek Syrian doctor Aretaios (at the end of the second century B.C.) also described attacks of asthma. Celsus (about 50 years A.D.) uses different terms for difficulties in respiration, such as dyspnea, orthopnea and asthma.

The Dutch doctor Jan Baptista van Helmont (1577-1644) was probably the first to emphasize the spastic state in asthma. He considered it a paroxysmal disease like epilepsy and suggested that it should be termed epilepsia pulmonum.

The English doctors Willis, Floyer, Cullen and Brée created the disease concept of asthma. Like van Helmont, Willis (1680) distinguishes between asthma pneumonicum and asthma convulsivum. According to him asthma pneumonicum is due to an obstruction of the bronchi, while asthma convulsivum is caused by spasms in the respiratory muscles. This spasm he assumed was produced through the nervous system. Floyer (1698) distinguished between asthma continuum and asthma periodicum. He thought that the cause of the latter condition was a contraction of the bronchi. Cullen (1773) calls Floyer's asthma continuum "dyspnea". The asthmatic paroxysm was considered by Cullen to be due to an increased flow of blood into the lungs. He also distinguishes a new form of asthma: asthma exanthematicum. The rash "invades" the lungs, a view which was also accepted by Floyer. Brée (1797) distinguishes between two types of asthma in the same way as Floyer. He considers that the attack is produced by the contraction of the respiratory muscles. Just as the organism strives to expel gallstones from the gall ducts by increased muscular activity, it endeavors to eliminate the cause of irritation from the bronchi. But,

in spite of these views and those of other authors, the conception of asthma was obscure. Investigators spoke of asthma hystericum, uterinum, carcinomatosum, haemorrhoidale, etc.

It wasn't until after Reissessen's discovery (1822) of the spiral arrangement of the smooth muscles in the bronchiole that the spasm theory took shape. A clearer view of the disease picture was given by Laënnec (1781 - 1826), who sharply differentiates asthma from other diseases attended by difficulties in respiration. Laënnec (1826) confirmed Reissessen's discovery of the muscle fibers in the bronchioli, and deduced that the asthmatic condition was produced by contraction of these muscle fibers in the finer bronchial branches. Williams (1840) and Wintrich (1845) studied the convulsive nature of asthma, the latter considering that asthma was due to spasm in the diaphram. Bostock (1916) and later Blackley (1865) studied the connection between hay fever and asthma. It was, however, Dunbar (1906) and Wolff Eisner who stressed most emphatically the significance of pollen and dust as the cause of hay fever and its connection with asthma. Trousseau (1868) regards the vasomotor rhinitis as a symptom of asthma and considers that it is found only in people who have, or are about to have, asthma. It was Trousseau and Salter (1868) who had perhaps first and foremost observed the allergic character of asthma. In 1871 came Leyden's discovery of the Charcot-Leyden crystals in sputum from asthmatic patients, which had been discovered 20 years earlier by Robin and Charcot in Leucemic spleen. In 1872 Weber advanced his theory. He considered bronchial asthma to be caused by vasomotorially induced swelling of the mucus membrane in the bronchi, and that it was caused by reflexively induced expansion of vessels. This view was based on the observation that the mucus membrane of the nose is vasomotorially swollen at the onset of the disease. It has the merit, as compared to the spasm theory, that it explains the expectoration. Moritz (1904) and later Strümpel supported this supposition.

In 1871 Voltioni advanced an entirely new doctrine. He considered polyposis of the mucus membrane in the nose to be the cause of asthma. He based his theory on the fact that asthmatic symptoms disappear after their extirpation. Fränkel (1881) considered that both nasal polyps and chronic rhinitis produced asthma. In 1882-83 Hack produced his "Schwellkörper" theory. He considered that the cavernous tissue in the nasal mucosa was an intermediate link between two reflex paths. By irritation of the throat, e.g. caused by a cold, reflex swelling of the cavernous tissue was produced, and, on the other hand, the swollen tissue in the nose produced a new reflex path to the bronchial musculature. By the removal of the intermediate link, the swollen mucosa, the reflex path was broken. Thus, according to Hack, it was chiefly a question of eliminating pathological processes in the nasal mucosa.

This view, of course, was not allowed to remain uncontradicted. A number of investigators, such as Fränkel repudiated it. Hack's theory, however, has the special merit of drawing attention to nasal diseases, not least in the causes of asthma. Schmeigelow showed that attacks of asthma could be stopped by placing a tampon of menthol of cocaine in the nose. He also stated that attacks of asthma could be precipitated by irritating hyperesthetic parts of the nasal mucosa, the so-called asthmogenous points.

Curschmann (1882), who detected the spirals which now bear his name in the sputum from asthmatic patients, considered that the spirals were formed as a result of an exudative bronchiolithism which induced emphysema by obstruction of the bronchioli. This state, according to Curschmann, precipitated a spasm of the finer branches of the bronchioli, which in conjunction with the formation of the spirals was, he considered, the cause of the attack of asthma.

In the eighteen-nineties, the physiologist Richet advanced his theory of anaphylaxis, which was further developed by Arthus' and Erlich's investigations, but it was with Pirquet's and Schick's (1903) doctrine of allergy that the present view of asthma as a hypersensitivity disease was finally put on a firm footing. The term idiosyncrasy is of an older date.

Widal, Rasch, Kämmerer, Kleewitz, Hansom, Storm van Leeuwen, Coca, Czerny, Monrad, Morawitz, Brügelmann, Siegel, Grimm, Rowe, Cooke, Baagoe and Salén are the names of some of the investigators who have contributed the most to our modern knowledge of asthma.

Salén observed an endogenous allergen in the mucus membrane of the uterus, thus showing that a hormonal mechanism may involve allergic conditions. Many investigators have taken the view that the precipitation of an asthmatic attack is connected with mental influences. Siegel (1912) in fact considers such influences to be precipitating factors. Talma (1898) - who may be mentioned in this connection - had previously been of the same opinion. He considered that the attack is caused by a spasm in the voluntary muscles of the air passages, as Brée and van Helmont had previously thought. This theory was also supported by Strübling (1906), who considered that intelligent people could imitate the same wheezing expiration as in asthma, though to a lesser degree. Talma's theory resulted in special therapy which is used to this day in the treatment of asthma, namely respiratory gymnastics.

Strümpel (1910) strongly emphasized that one must be cautious in assigning neuropathic causes. The present view likewise seems to be that psychic influences cannot evoke the asthmatic condition, but that they may affect the disease picture when the disease has existed for some time.

Among other interesting and elucidating investigations mention may be made of Besnier's. In 1892 he described as prurigo diathésique a disease characterized by intense itch, localized especially in the bends inside of the elbow and behind the knee. He drew attention to the fact that the disease was constitutional and often appeared together with asthma and intestinal diseases. Rasch (1903) defined the disease more closely and proposed that it be called prurigo Besnier.

Morawitz (1921) considers that asthma is produced by hyperirritability of the nervous system. Eppinger and Hess considered that asthma is due to an increase in the tonus of the autonomic nervous system, especially the vagus.

In asthma, hereditary factors doubtless play a certain role. As a rule there is also a predisposition for certain other diseases. According to the French school, this predisposition consists of an arthritic diathesis, a hereditary condition involving an abnormal reaction to irritants which do not precipitate diseased conditions in healthy people. Arthritic diathesis is stated to involve a predisposition for various diseased conditions, such as eczema, urticaria and psoriasis, as well as for certain disorders of metabolism, such as gout, adipositas, diabetes and also certain nervous diseases such as migraine.

In Germany, Czerny (1908) launched the term exudative diathesis, which according to him is a congenital and constitutional anomaly, the symptoms of which depend on the diet. He considers that the anomaly consists in a disturbance of the fat metabolism. The symptoms especially take the form of exudations from the skin and mucus membranes. In the exudative diathesis Czerny also includes disease conditions of a neuropathic basis, such as asthma and urticaria. Monrad (1921) points out the importance of exudative diathesis and the diet.

Coca (1920) states that idiosyncrasy in man is caused by a non-protein substance, for example aspirin. He proceeds from the assumption that such substances directly tend to precipitate the attack. Attempts to show antigen characters in these substances have hitherto given negative results. On the other hand, the attempts were successful when the substance was connected with a protein. Storm van Leeuwen has devoted much work to this question, and has moreover distinguished the group among asthma patients, who are hypersensitive to acetyl-salicylic acid. His name is perhaps best known in connection with the activity of allergens in the air.

This historical résumé does not claim to be exhaustive as the studies on asthma during the last few years have been prolific. Only the principal theories and discoveries could be mentioned.

INCIDENCE

Asthma is a very prevalent disease. It occurs in persons of all ages and races. The sexes are about equally affected. It isn't a rarity, by any means, even in infants and is fairly frequent in children, the number increasing with the years of the patients. 20 - 30 % of asthma in childhood begins before the age of two.

Characteristic symptoms rarely appear at birth, but are seen; approximately the same number of infants are affected by asthma from birth to 3 months; twice that number are seen from 3 months to one year of age. After that, the number increases steadily.

Only during the first year, La Fétra found a predominance of females. After this, males are afflicted much more than females.

ETIOLOGICAL FACTORS

Asthma often shows a strong hereditary tendancy. The bronchiolar spasm may be (a) of a reflex nature and due to the stimulation of hypersensitive afferent vagal endings in the larynx, or of trigeminal fibers by some nasal abnormality: the bronchoconstrictor impulses travel via efferent vagal fibers, (b) in allergic phenomenon, i.e., the result of sensitization to some foreign protein. This is the most common cause of the conditions, e.g. hay fever, urticaria or eczema either in the patient or in members of his family. The foreign protein may be inhaled or may be some kind of food or the protein of bacteria in the respiratory tract. The sensitivity of certain individuals to foreign proteins presents many features common to anaphylactic shock in animals. The two conditions are probably in some way clearly related. Sudden death may result from the injection of horse serum (e.g., diphtheria antitoxin or anti-tetanic serum) into an asthmatic subject. A guinea pig when injected with a protein to which it has previously been sensitized dies rapidly from shock. The bronchiolar muscle is strongly contracted. The air is trapped so that the lungs are maximally distended and do not collapse when the thorax is opened. Even when the pulmonary tissue is deeply incised the air does not escape from the distended lung. This manifestation of anaphylaxis is associated with, perhaps due to, the liberation of histamine into the pulmonary circulation. Thornton, among other workers agrees that histamine appears in the blood promptly after the administration of the antigen and persists for a brief interval.

Cerqua found a marked increase in blood histamine following an attack. The histamine theory is very attractive and would be accepted by most workers if the use of antihistamines would show better than a 20 - 40 % improvement of the patients' symptoms.

It is well known that anaphylaxis and histamine administration produce almost identical effects in the guinea pig. Histamine producing bacteria have been reported in the bronchial secretions of asthmatics.

Since asthma can be essentially considered an allergic disease, it can also be regarded as primarily a disease of adaption. It is often caused by non-specific (e.g. emotional) stress and sometimes prolonged remissions can be obtained by non-specific therapy, for instance with insulin shock. It is difficult to explain why in other cases shock therapy (e.g. electro-shock) actually aggravated the asthmatic state (Cohen & Holbrock) but this same inconsistency in the effect upon asthma has been noted in patients treated with ACTH. In most instances ACTH greatly ameliorates the asthmatic condition but occasional attacks of asthma are actually precipitated by this hormone. Significantly, the urinary excretion of histamine and histadine rises in asthmatics, during remissions caused by ACTH (Rackemann).

The anti-asthmatic effect of the gluco-corticoids and of adrenergic substances suggests that endogenous discharge of adrenal hormones may be a normal defense reaction against this abnormal or allergic response to certain agents. An inadequacy of this response may well play a role in the pathogenesis of asthma. These observations, among others, induced research into the possible relationship between asthma and the "General-Adaptation-Syndrom" (Seyle).

It has been shown that, as mentioned above, that emotional stress could precipitate an asthmatic attack. This is generally believed to be a good indication that asthmatic attacks fit into Seyle's definition of "stress reaction".

Cecil & Loeb suggests the following etiologic classification of asthma:

Asthma beginning before age 30:

Extrinsic asthma
Simple allergy
Dusts
Pollens
Molds
Animal danders
Occupational dusts
Household dusts

Foods
Drugs

Simple allergy may be complicated by:
Infection
"Depletion"
"Asthmatic bronchitis"
Vasomotor rhinitis

Predisposed persons can be divided into two groups - the young and old. One can assume that when it begins before age thirty, the cause is allergy unless proved otherwise: But when it begins after age forty, the cause is not allergy unless proved otherwise (Cocke). The young people are hypersensitive to some foreign substance, usually a dust, occasionally a food or a drug; the cause is outside their body - it is "extrinsic". The history will show that the asthma occurs only in certain places, or during certain times of the year. It may be related to contact with animals, to certain houses or rooms, or to certain occupations. The asthma clears on admission to any hospital. In older people, the cause of asthma is usually something inside the patient and therefore it is "intrinsic". Although these intrinsic factors play a very small role in children they must be considered.

Intrinsic asthma
Bacterial allergy
"Depletion"
Somatic
Infection
Malnutrition
Psychic
Polypoid sinusitis and asthma
Emphysema - primary or secondary
Tumors - foreign bodies

Simple allergy means that symptoms occur only when the patient comes into direct contact with the particular agent to which he is sensitive, and then clears when the contact is broken. Contact may be brought about by inhalation, by ingestion, or by injection into the skin. Or these various methods, inhalation of dusts is by far most important in adults, while ingestion of foods plays the important role in children.

Dusts which may cause asthma by inhalation are of many kinds; pollens make up a large and important group. Trees, grasses and weeds may be important, but their relative value depends on their location. Trees produce pollen in quantity, but each for only a few days in May. Tree pollen asthma is rare, although it may be severe. Grasses begin to pollinate in late May, and grass pollen is demonstrable in the air until after August 1. Many patients have hay fever and asthma from grasses. The ragweed pollen is the chief cause in these sufferers.

Danders and Emanations from Animals constitute another important group of etiologic agents. Cat asthma is common Dog asthma much less so. Horse asthma was common before the era of the automobile but it is now rare. Feathers in pillows may cause trouble if they are dirty and old. New feathers aren't as bad.

Molds, notably the fungi of the imperfect genera, produce spores in large quantities, especially in late summer and fall, and play a part in certain cases.

Occupational dusts constitute an important group. Bakers and housewives may have asthma from wheat flour. Cotton, wool, leather, malt, orris root, ipecac, flaxseed and glue have been described as the cause of asthma, and the list grows with the development of complex chemicals used in modern industry. Dyes, solvents, bleaches, developers, fixatives and other substances may cause allergic symptoms, usually of the skin. Occasionally they can cause asthma in children since they are exposed to the dusts of their parents' clothes. Today, the modern Layette is composed of so many more and complicated things that it is easy to understand why the young sensitive child can develop asthma much sooner than the child of fifty years ago.

Household dusts represent, from the practical view-point, the greatest cause of trouble. This is, however, on the decrease since the advent of sponge rubber which is being used as mattresses, pillows and upholstery. This cuts down a large part of the irritative dusts in the house which cause asthma.

Foods may cause asthma, especially in children. Eggs. wheat and milk are the usual offenders.

Drugs may be mentioned. Salicylates, sulfa drugs, penicillin and more rarely the barbituates may cause asthma in the hypersensitive person although the usual reaction to the drugs is a dermititis.

Persons who are predisposed to allergy have the capacity to develop sensitiveness. Multiple sensitiveness can be expected and many patients are found sensitive to pollens, animal danders and other substances all at the same time.

The simple allergy may become complicated, so that the asthma persists after contact with the allergen is broken. Secondary infections of sinuses or bronchi will do this, and a few cases such general disturbances as fatigue, anxiety or poor condition may aggravate the simple cause.

"Asthmatic bronchitis" is a useful term applicable to many cases, especially in young people. New head colds precipitate the attack, and the patients wheeze, evidently because the infection lowers the threshhold to make a slight

allergy effective. One often finds that when a cat has been removed, new colds no longer cause asthma. Attacks of asthmatic bronchitis may occur only once or twice a year, or may recur every few weeks.

Vasomotor rhinitis of a severe chronic sort occurring in young adults, may lead to asthma, and this asthma is often severe.

Intrinsic asthma isn't caused by allergy but is something that the patient carries with him in spite of changes in season, residence, occupation or diet. Since the cause is unknown, these patients are difficult to treat.

Bacterial allergy indicates a theory to explain those many cases in which asthma follows new head colds, and occurs without regard to change in environment. The acute cases are quite similar to the group described as "asthmatic bronchitis"; here however, the inciting cause must be ascribed to the infection itself.

"Depletion" as a cause is much more interesting and important. One can recognize patients who have lost weight, strength and especially courage from one of many causes, and in whom asthma develops as a result. The support of this idea lies in the great improvement, and sometimes "cure", which follows when the depletion is corrected.

"Depletion" may be somatic, it may be psychic, it may be both. Somatic depletion has various parts. Focal infections can cause asthma. Infections of the appendix, gallbladder, prostate and tonsils have been causitive. Constipation, malnutrition and anemia have been important in still others. A thorough examination, with care for and of the patient as a whole, is essential.

Psychic depletion is common. It can be considered under the title of Psychosomatic Medicine. Clinically it includes two general topics: (a) Those cases where the symptoms referred by the patient to one or the other of his physical symptoms and purely the result of some emotional disturbance and (b) those where the emotional disturbance has played upon some physical locus minoris resistentiae and precipitated the disorder.

The importance of such a delineation is to call our attention to the close relationship of mind and body, and especially to impress physicians that many of the symptoms that they have been accustomed to treat along physical lines are really of psychological origin. For example, in the past, it has commonly happened that symptoms referred to by the patient as indigestion were accepted as such by the doctor and labeled "dyspepsia", which was then treated as a purely physical disorder, although no physical lesions were demonstrable. In this way, the doctor

gives form and substance to the syndrome in a patients' mind, and in this way psychoneurotic invalids who were complaining, improving a little and always relapsing, were created in considerable numbers.

In general, it appears that either emotional trauma or continued emotional tension will, in people of a certain temperament, facilitate the appearance of certain organic diseases; but there is probably a local predisposition as well toward these organic diseases, because people of similar temperament exhibit different localizations of their somatic lesions.

The types of temperament that are mainly concerned appear to be anxious, over-conscientious types and the covertly aggressive. It appears, in fact, that whatever the temperamental and characterological aspects of physical diseases or peculiar physical dysfunctions are investigated, the traits recorded are very similar. This Ryle (Lancet, 1939, 297) speaking of the "visceral neuroses" says, "Its victims (of spastic colon) are industrious and conscientous", and he mentions emotional signs in more than half of his examined cases. This is not to say that their temperamental traits are the "causes" of their organic disturbances; but rather that the constitutional pattern shows itself on the one hand in the temperamental and on the other hand in the physical sphere; although there is doubtlessly interaction between the two.

Foreign bodies and Tumors must be included in any classification of the causes of asthma. There are occasional cases, especially in children, in which persistent asthma depends upon a foreign body inhaled. Not to remember that foreign bodies and tumors can cause asthma, which may simulate closely the ordinary cases, may be a fatal mistake.

Polypoid sinusitis is given separate designation, chiefly because there is a small but typical group of older patients whose asthma is accompanied by a nasal quality of the spoken voice, due in turn to obvious involvement of the paranasal sinuses. Lesions of the sinuses, varying from thickened membranes to fullblown parasinusitis, may be found in any age group in asthmatics of all types, but in this older group it predominates.

PATHOLOGICAL PHYSIOLOGY AND THEORIES OF DYSPNEA

Asthma is a paroxysmal disease in which acute anoxia is caused by spasm of the smooth muscles of the finer bronchioles. Edema of the bronchiolar mucosa is probably also present. The alveoli are poorly ventilated and some may be entirely cut off from their supply of air. The high percentage of carbon dioxide and the low

percentage of oxygen in the alveolar air results in low oxygen saturation of arterial blood and the retention of carbon dioxide. This gaseous acidosis is met by excretion of a highly acid urine and a rise in the alkali reserve. An intense cyanosis can develop if the attack is severe enough. The continued stimulating effect of oxygen want and carbon dioxide excess upon the respiratory mechanisms causes violent hyperpnea mediated through the carbon dioxide sensitive centers in the medulla oblongata.

The greatest respiratory distress is during the expiration because there is a natural tendency for the bronchioles to narrow during expiration and dilate during inspiration. Therefore the greatest effort is exerted during expiration. The respiratory muscles contract with great force and the accessory muscles contract and are brought into play. The expiratory muscles contract in the attempt to express air from the lungs. The intrapulmonary pressure is greatly elevated and the air escapes through the constricted tubes with a distinct wheezing sound. Owing to the difficulty and prolongation of the expiratory phase, normal deflation of the lungs cannot occur before the next inspiration begins. The lungs, therefore, remain almost maximally expanded even at the end of expiration. That is, during the asthmatic paroxysm a very large volume of residual air is present in the lungs. The volume of tidal air is greatly reduced and corresponds to the vital capacity at the moment. Since the subject is already exerting the greatest inspiratory and expiratory efforts of which he is capable, there can be no supplemental or complemental air. The changes in volume in the overdistended lungs are very small and not commensurate with the movements of the thoracic walls. As a result, the high intrathoracic pressure induced during inspiration causes the structures at the root of the neck to be drawn toward the thoracic cavity to take up the space which the lungs are unable to fill. The structures are expelled again during expiration. The veins of the neck and face become engorged. The restricted movements of the lung also greatly reduce the effect of mechanical mixing upon the lung air, the slower process of diffusion being depended upon to a larger extent for the freshening of the alveolar air.

Repeated asthmatic attacks during early life, while the thoracic framework is still soft, produce a characteristic deformity of the thorax. The chest is fixed in an elevated position, resembling the normal chest in full inspiration. The sternum is prominent and the ribs more horizontal than normally. The anterioposterior diameter of the thorax is as great or greater than the lateral, the chest assuming the so-called barrel shape.

F. Wyss, E. Lopez-Cotet and F. Schmid of the Inselspital Poliklinik of the University of Bern, under the direction of Professor W. Hadorn, have shown with their experiments on the pneumokymograph in 1952 that still another factor is important

in the production of the asthmatic dyspnea. In their experiments they have demonstrated that the expiratory phase of respiration can be divided into two parts. The first part is the same in normal and asthmatic individuals. A rather sudden increase in the expiratory effort which must be caused by an augmentation of tonus in the inspiratory musculature, especially the diaphram, causes the increased expiratory effort (dyspnea) in the second phase. Weltz has shown this to be true with a rontgenkymograph.

The diaphram therefore relaxes to its position at the beginning of inspiration. Then, because of its increased tonus, cannot relax anymore and will, only through the pressing of the abdominal musculature with increased effort, be driven any higher. This appears in the second, slowed phase of expiration.

PATHOLOGY

The lesions in the lungs or asthmatic victims dying during an acute attack consists mainly of vesicular emphysema and of thickening of the walls of the bronchi and bronchioles and obstruction of their lumina by dried and hardened mucus. In cases uncomplicated by infections, the main lesion is hypertrophy of bronchiolar muscles. In the other cases the important lesion was hypertrophy of the mucus glands. The trachea and large bronchi are little affected and, at most, show diffuse reddening of their lining. Thickening of the bronchi is due to edema, cellular infiltration, and fibrosis which affect all layers. The epithelium shows increased height and pseudostratification. Desquamation is usually moderate and ulceration absent in cases uncomplicated by secondary infection. The basement membrane of medium sized bronchi is thickened and hyalinized. The glands are large and show evidence of increased production of mucinous secretion. The connective tissue of the mucosa and submucosa shows moderate edema and is infiltrated by lymphocytes, monocytes, and eosinophiles. The muscle is usually found in a state of contraction, but whether it commonly shows true hypertrophy is a matter of dispute. Eosinophiles are extremely numerous in some cases but few or absent in others.

The mucus which fills the lumina of many of the tubes contains desquamated epithelial cells, monocytes, and eosinophilic leucocytes in variable numbers. Toward the end of an attack, these masses are coughed up and expectorated. The content of the sputum varies, but practically always shows plugs of hardened mucus, monocytes and macrophages, degenerated epithelium cells, and some leucocytes. The more pathognomic elements are eosinophiles, Curschmann's spirals, which are twisted spirals of mucus from the bronchioles, and Charcot-Leyden crystals,

the origin and nature of which are unknown. In the parenchyma of the lungs there is much hyperdistention, with rupture of alveolar wall in many places. The enlargement of air sacs is unaccompanied by any thickening or fibrosis of septa unless the lung has been the site of an inflammatory process. Sometimes the emphysematous tissue is interspaced with small patches of atelectasis resulting from long standing complete obstruction of small bronchioles.

Death from asthma rarely occurs from uncomplicated cases. The inflammatory thickening of the mucosa and obstruction of the lumina by thick tenacious mucus are of the greatest importance in fatal cases than is bronchiolar spasm.

Asthma in children as the cause of heart disease during later life has been shown not to be an important factor. In a series of cases, it has been shown by Derbes and Engelhardt that after the average duration of 4 1/2 years of the disease, children showed no enlargement of the heart or great vessels. The E.K.G. was also normal.

In summing up, it has been shown that the causes of asthmatic dyspnea are three in number:

1. bronchiolar spasm.
2. swelling of the bronchiolar mucus membrane.
3. increased tonus of the inspiratory musculature, especially the diaphragma.

SYMPTOMATOLOGY

During the attacks, whether separated by long periods, or occuring every few hours, there is the same wheezing, whistling breathing, and dyspnea, all the accessory muscles of respiration being called into requisition. The patients are usually relieved by sitting up or by having the shoulders raised and the elbows braced so as to give better support to the muscles passing from the head, arms and shoulders to the chest. There may be cyanosis. In infants and young children there is, at each inspiration, sinking in of the suprasternal and supraclavicular fossae and of the rib insertions of the diaphragma below; while in older children or in protracted cases the whole chest moves upward with even less expansion. Toward the end of a paroxysm the chest may be temporarily barrel-shaped; but after the attack has passed the emphysema disappears and the chest resumes its normal shape. Repeated or prolonged attacks produce a permanent deformity. The respiratory rate in infants may be anywhere from 44 to 80 per minute, and with the alae nasi dilating, beginning bronchopneumonia is suggested.

Palpation reveals bronchial fremitus in most cases.

Percussion early in the paroxysm elicits a note that is somewhat dull; toward the end of the attack the note may be hyperresonant.

Auscultation in the uncomplicated cases reveals dry squeaking or whistling, along with some musical or sonorous râles, both during inspiration and expiration; the inspiratory sounds are the louder, while the expiratory sounds last longer. These sibilant and sonorous râles may be simultaneously heard all over the chest or at different parts in succession, coming and going during the attack. Often the pandemonium of the chest can be heard at the distance of 20 - 30 feet, even in the infant. Notwithstanding all the adventitious noise, the breath sounds themselves are actually feeble because of very little air entering the chest. Toward the end of an attack, and in cases complicated by bronchitis, there are subcrepitant and mucus râles.

Cough, if present, is short and dry, except toward the end of an attack, when it is looser. In older children there is some expectoration. The characteristic crystals and spirals are present in the sputum.

Spontaneously, or after the administration of some sedative, the respiration becomes less and less noisy, and less rapid. The sibilant râles are replaced by larger sonorous and mucus râles, and soon only large moist râles and sonorous breathing remain to signalize the storm that has passed. The hyperresonant note disappears and the chest resumes its usual shape and normal respiratory rhythm. The temperature in uncomplicated cases is rarely above normal, except in infants, where it may rise to 100 or 101 degree fahrenheit.

The leucocytes are usually, but not always increased, as in bronchitis, but a differential count of the white cells shows what does not occur in bronchitis, a constant and usually marked increase in the number of eosinophiles. This eosinophilia is greatest in any given patient at the height of the attack; it disappears in the intervals, but in the subacute cases a low grade eosinophilia persists. Thus the differential count of the leucocytes is of diagnostic and prognostic value, so far as the attack is concerned.

DIAGNOSIS

Asthma in infants may simulate bronchopneumonia or a fine bronchitis in their early stages when there is little or no secretion, rapid labored breathing and feeble respiratory murmur, but the low temperature, and the dry whistling râles that flit from one part of the chest to another will suggest the real diagnosis. If such symptoms follow or accompany gastric indigestion, urticaria or attacks of sneezing,

asthma is all the more probable The existance of eosinophilia, together with speedy recovery from the attack, and later recurrences will confirm the diagnosis.

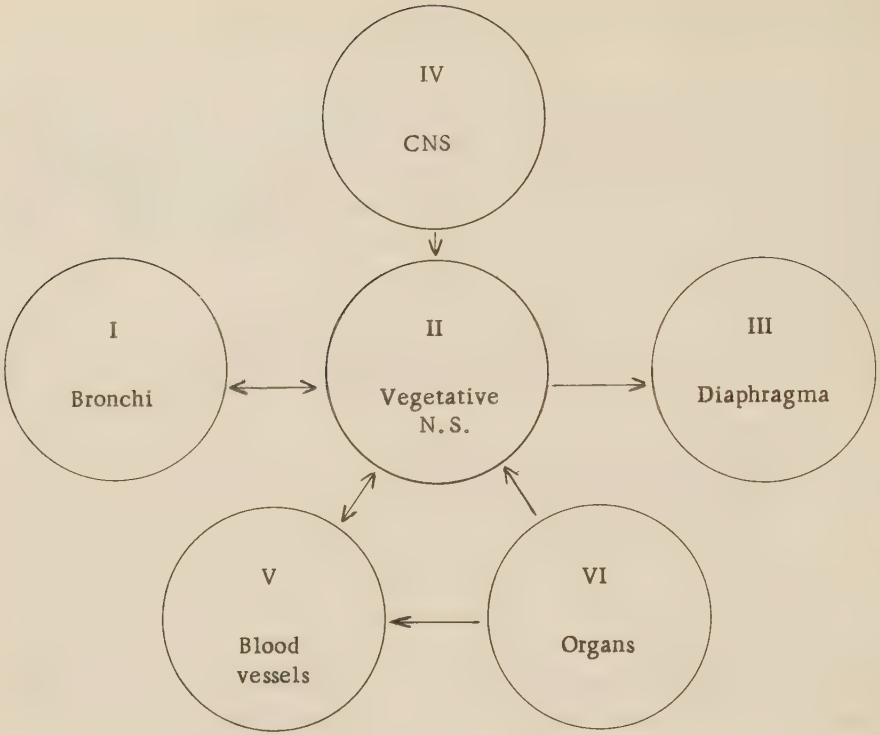
It is a mistake to make a definite diagnosis of asthma on the basis of an isolated attack of dyspnea accompanied by the proper objective findings. Only repeated occurrences of such a syndrome, especially if preceded by or accompanied by eczema, urticaria, or repeated so-called colds or vasomotor rhinitis, should arouse one's suspicions.

DIFFERENTIAL DIAGNOSIS

1. Obstruction due to foreign bodies
2. flaccid epiglottis
3. mediastinal masses
4. congenital heart disease
5. bronchial infection
6. Croup
7. Pertussis
8. Tuberculosis
9. cystic fibrosis of the Pancreas

TREATMENT: GENERAL SURVEY

In recent years, the physician's armature of drugs to be used in the treatment of asthma has increased a hundredfold. In this paper we are mainly concerned with the use of Niacin amide (N.A.). However, Dr. Wyss of the Inselspital Poliklinik whom I have previously mentioned, has written an excellent summary of the different methods and approaches in the treatment of asthma. The following chart has been reproduced from Dr. Wyss' work in its entirety.



I The influence of a disease process in the bronchi.
Allergen withdrawal, specific and unspecific desensitization,
Anti-histamines
ACTH, Cortisone, shock therapy, fever cures, stimulation through x'ray
Broncholytica, Atropin, Potassium iodide, "Bronchial toilet"

II Arresting the vegetative reflex, bronchus - diaphragma.
Ganglion-blocking agents? Nerve operations (vagus, sympathetic)
High climate

III Treatment of the inspiratory cramp of the respiratory musculature.
Respiratory gymnastics, Electrolung, Pneumoperitoneum

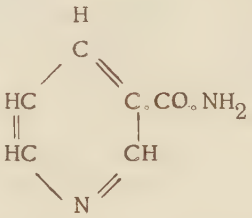
IV Influencing the asthmatic state thru the central nervous system
Psychotherapy, Sedatives

V Influencing the blood vessels
Adrenalin, Nor-adrenalin, Pituitrin, Ephedrin, etc.

VI Treatment of organic diseases
Nutrition, Hormone therapy, cleaning of infective foci

NICOTINE AMIDE: ITS PHARMACOLOGICAL AND CLINICAL PROPERTIES

Nicotine amide (N.A.), U.S.P.; (Nikotinsäure amid, Bayer; Niconacid, Dr. Wander; Nicobin, Merck; P-p Factor, Niacin amide) is a white crystalline powder with a slightly bitter taste. It is soluble in water (1 : 1), producing a neutral stable solution. The compound is a pyridine-3-carboxylic acid amide:



It is a nutritional factor effective in the treatment of human pellagra.

PHARMACOLOGICAL EFFECTS

Nicotinic acid evokes vasodilation. Given orally or parenterally, doses of 30 mg. causes a distinct flushing of the face and neck and a transient fall in blood pressure. N.A. doesn't produce the vasomotoric effects of its close chemical relation, nicotinic acid (Niacin).

Maisel and Somkin (1942) used nicotinic acid successfully with epinephrine or ephedrine in the treatment of asthmatics. Melton, in 1943 administered doses of from 50 - 100 mg. nicotinic acid intravenously to patients with asthma and observed some clinical improvement.

The therapeutic use of nicotine amide (N.A.) for allergic diseases is based upon the experimental work of Businco 1941, Schupfer 1942, Halpern and Dainow 1944, Butturini 1946, Alechinsky 1947 and Frommel and his staff in 1947.

Dainow, with intravenous injections of 0.1-0.2 grams or 0.3-0.4 grams orally of N.A. daily attained quick improvement with asthma, hay fever and different skin affections. He also showed that continual treatment, if it didn't cure the disease, prevented it from getting worse. He, however, attained the best results in the treatment of the congestive dermatological conditions. A series of cases, both male and female, of all age groups were treated with N.A. for a period of two

years. His results were much better than when he used Euphonyl. Calcium, Opocalcium and serum for the same period of time.

During this period of work, Dainow thought that, because of his excellent results, that there might be some correlation between N.A. deficiancy and the allergic condition. He showed that although there was some interrelationship, the correlation wasn't definite.

In later papers Halpern and Dainow have shown that N.A. has a definite antagonism toward acrosol histaminic inducted asthma in guinea pigs, where it doesn't have this effect in asthma produced by acetylcholine.

They have also demonstrated the antagonistic action between N.A. and the histaminic action on the intestine and uterus of the guinea pig (spasmolytic). Of interest is the fact that it does oppose the acetylcholine action here.

Since there is a close interrelationship between anaphalactic shock and asthma, they decided to try and oppose the anaphalactic contractions of the intestine and uterus of the guinea pig. They were successful in opposing the intestinal contractions, but not those of the uterus.

These two workers, therefore, demonstrated in 1944 the anti-histaminic activity of the amide of nicotinic acid. E. Frommel, A. Bischler, I.T. Beck, F. Vallette and M. Favre, also of the University of Geneva have shown essentially the same results in 1947.

Also in 1947 Krause published a paper showing that Nicotine amide (N.A.) can be used successfully in the treatment of Serum Jaundice. 10-20 minutes after the first tablet, the patients felt a decrease in itching. In 4-6 hours, the exanthema disappeared along with the rest of the itching. He also recommends the use of small doses after the disease is over to prevent recidivation.

In 1951 Alechinsky also verified the work of Dainow and Halpern of 1944. He found that 100 mg. of N.A. protected guinea pigs against death from injections of lethal doses of histamine, further demonstrating the antihistaminic activity of N.A.

Also in 1951 Hulskämper used the drug together with calcium bromide and norephedrine with good results.

Baker in 1953 recommended benzyl-nicotine amide together with isopropylarternol in the treatment of asthma.

Businco, who originally showed the antihistaminic activity of nicotine amide (N.A.) in 1941, repeated this fact at the International Congress of Allergy in 1952. At the same congress, Saurer reported just the opposite activity for N.A.

CLINICAL RESULTS OF NICOTINE AMIDE THERAPY AND 5 CASE HISTORIES

In the Jenner Kinderspital of the University of Bern, Prof. Dr. E. Glanzmann, the director, has used N.A. under the trade name of "Vi-Nicotyl" (Dr. Wander) with an "asthma mixture" that is composed of the following:

Ephetonin.	0.2
Phenobarbital. Sol.	0.2
Bellafolin pulv. c. Saccharol (1.5% Alkaloid)	0.05
Potassium iodide	1.0
Elix. pectoral.	2.0
Sirup Althaeae	40.0
Aquae dest. ad	100.0

The following cases have been selected as good examples of the use of N.A. in the treatment of bronchial asthma.

Case No. 1: Sch., Hans Ruedi.

This is the first admission of a normal 5-year old male. His chief complaint is that of respiratory distress. His past history reveals that when he was 7 weeks old he developed an exudative skin eruption on his face. At the end of his first year, the dermatitis improved, but with this improvement, he developed asthma. The eczema lasted for 4 years. Because of the asthma he was sent to Beatenberg, Switzerland for 4 months, but there was no improvement. Later he developed a strong cough with the asthma. In autumn, 1951, he returned to Beatenberg and, because of repeated injections, showed a great deal of improvement. While he was there, his parents were told that he had tuberculosis. The child has also had varicellen, measles (3-4 year) and pseudocroup.

His mother and father have tuberculosis. His mother had eczema for a long time and two of her brothers have asthma; one with severe attacks.

Upon admission the child proved to be in good general condition. He had an obvious inspiratory and expiratory stridor of grade IV. He couldn't talk because of dyspnea. On physical examination, there were no signs of eczema. He had a barrel-shaped chest and a short neck His heart appeared a little enlarged. The lung borders were diminished and movable. The diaphragma was very deep. Percussion yielded a hyperresonant tone over the entire lung area. By auscultation one heard a great many scattered râles, such as whistling, etc. Dyspnea was present with forced breathing or when he talked too long. The liver was just palpable.

Tonsils were enlarged. By fluoroscope the lung fields showed an increase in density. The hili showed indications of a pathological process, especially paracardially. The blood pressure was 115/75-0.

The therapy upon admission was:

6 x 5 ccm. asthma mixture
3 x 1 tablet Vi-Nicotyl

Progress notes:

4 days after admission the child was decidedly better.

He had the following white blood count:

Total	10,000
Neutros.	34 %
Lymphos.	41 %
Monos.	10 %
Eosinos.	13 %

After 12 days, the boy showed only a slight increase from normal in the length of his expirium and a few scattered dry râles. On the 22 day he had absolutely no signs of asthma. On the 31 day, he was discharged as highly improved. His white count was as follows:

7,200	Leucocytes
34.5 %	Neutros.
46.0 %	Lymphos.
4.0 %	Monos.
13.0 %	Eosinos.

He also had a positive Pirquet and Moro.

Case No 2: Zür., Niklaus, 5 years old.

The chief complaint of this boy on admission was difficulty in breathing and abdominal pain. His past history shows that when he was 9 months old he developed eczema which, when he was a year and a half old, improved. Since then he has suffered from repeated "colds" accompanied by exudative skin changes on the extensor sides of his arms. A year previous to admission he had a measles-like skin eruption for approximately one week. A week before admission he had an attack of rhinopharyngitis without fever. That evening he had difficulty in breathing. His respiration was asthmatic in character. The next morning his breathing was even more difficult. The doctor couldn't hear any breath sound and had a tympanic note upon percussion of the entire lung area. He was sent to the hospital with the suspicion of a spontaneous pneumothorax.

On admission the boy breathed irregularly and with some effort, more so on expiration than inspiration. He wasn't cyanotic. He had lichenified areas on the extensor side of the right thumb. Indolent lymph glands were present on the jaw

angle and the thyroid was slightly enlarged with decreased consistency. Discrete residual of a ricketial rosary were present. His blood pressure was 98/66. The lungs yielded hyperresonant percussion sounds. The breathing sounds were present and easily heard. The expirium was prolonged and dry whistling râles were heard over both lung areas. The excursion of the right lung was a little less than the left. His nose was congested preventing nose breathing; tongue was a little coated; tonsils were hypertrophic, cryptic and a little inflamed with no coating; from the epipharynx flowed a rich mucoid secretion; the pharynx walls were also inflamed. By fluoroscopy the right diaphragma showed shorter excursions than the left. The lung fields showed a slight increase in transparency with no verification of a pneumothorax. The admitting diagnosis was rhinopharyngitis and asthmatoid bronchitis.

He was given: 400,000 units penicillin
asthma mixture 6 x 1 teaspoon.

The next day he was given 500 mg. Redoxon and 3 x 1/2 tablet Vi-Nicotyl. His asthma was much better except for the persistence of a slightly prolonged expirium. 4 days after admission there was just a little coughing and his nose had improved. Pharynx and tonsils weren't inflamed. Over the lung areas there were still isolated bronchitic sounds. 9 days after admission the child was discharged, with a little cough and no rhinopharyngitis, as much improved.

Case No. 3: G., Ruth.

This is the first admission of a 6-month old female of normal development. Her chief complaint is asthmatic bronchitis. 2 months before admission she had the grip, lung inflammation and asthma which lasted 12 days. She was treated with penicillin and cured. 10 days before admission she had fever, asthma and a cough. She improved, but 6 days before admission the infant appeared tired and apathetic. The next day she had temperature which slowly increased until, by morning of admission she had 39.5° C. Her doctor gave her suppositories which improved the asthma. Just before admission the doctor also gave her: 2 x 300,000 units penicillin.
1 weak A.P.C. suppository
Ephetonin suppository
Mustard plaster

Upon admission we saw a normal 6-month old female with dry, pale skin which had a decreased turgor. Her temperature was 40° C. Her gaze was rigid and she had twitching of both her hands and face. Her pupils were isocoric, wide and reacted promptly to light. Reflexes were very lively. The lung borders were normal. Breath sounds were sharper than normal especially right posteriorly. Expirium prolonged with a great many dry râles over both lungs. The tongue, pharynx and tonsils were inflamed.

Blood picture was:	R.B.C.	4.45 million	Stab	2.5 %
	Hb.	81 %	Segmented	31.5 %
	F.I.	.92	Lymphos.	60.5 %
	W.B.C.	8,400	Monos.	4.5 %
			Eosinos.	.5 %
			Basos.	-
			Plasma	.5 %

Therapy on admission was: 6 x 100,000 units penicillin
Coramin and sympathol interchanged every 4 hours
1 ampule Vi-Nicotyl I.M.
Tea

The day after admission she was much better and her temperature was 37.5° C. The cough was still hard and a small-spotted exanthema appeared and disappeared on the extremities, neck and sternum. On the sixth day there wasn't any fever, but the asthma was worse. From then on she received 1/2 ampule of Vi-Nicotyl. On the 12 day her blood picture was:

R.B.C.	4.27 million	Stab	0.5 %
Hb.	95 %	Segmented	9.5 %
W.B.C.	7,800	Eosinos.	3.5 %
		Lymphos.	80.0 %
		Basos.	-
		Monos.	6.0 %

14 days after admission the asthma was still present with changes in intensity. There was no temperature. Vi-Nicotyl was increased to 1 ampule and asthma mixture was given. After 22 days the infant was discharged as improved.

Case No. 4: Ga., Rolf

This the first admission of a 3-year old normal boy whose chief complaint was difficulty in breathing.

He has been a little constipated ever since birth. 2 days before admission he complained of abdominal pain and had 38° C. temperature. He suddenly started to cough and then turned white and collapsed. His doctor gave him penicillin, Elkosin, A.P.C. suppositories and Resyl sirup. The child then vomited and coughed up a great deal of mucus.

His older brother and his grandmother on his mother's side have asthma. The rest of the family history is without significance.

He was admitted with the diagnosis of Asthmatic bronchitis and the therapy upon admission was: Asthma mixture
Mustard plaster

He presented himself on admission with a dry cough. His skin was dark with a few scratch effects and blue marks. The entire physical examination showed nothing remarkable except the lung findings. Loud percussion sounds with diffuse bronchetic râles along with dry râles were found in both lungs.

The lung findings improved a great deal and the cough had almost disappeared 2 days after admission. He then received 3 x 1/2 tablet Vi-Nicotyl because of a family history of asthma. 12 days after admission he was discharged as cured and was to keep on using Vi-Nicotyl 3 x 1/2 tablet.

Case No. 5: Buf., Daniel.

This is the first admission of a 3 1/2-year old boy who has obvious respiratory stridor, both inspirational and expirational, whose chief complaint is respiratory difficulty.

After a normal birth with a slight Icterus neonatorium, he developed an exudative eczemoid skin eruption when he was 2 months old and which developed into eczema. He couldn't eat milk or eggs. When he was 6 months old, he developed asthma which, at first, responded to Neoton and Recto-calcium, but which later didn't respond to the Recto-calcium. He then developed a sensitivity to his diapers and to tomatoes.

His mother has both asthma and eczema and his maternal grandmother had had hives. Other members of his mother's family have asthma and a tendency toward urticaria. His paternal great-grandfather, had asthma.

The child's physician said that he reacted well to Sulfonamide and Asthmolysin. After he had contact with Pertussis, he got Aureomycin and after that had an asthmatic attack that lasted 3 weeks. He was then admitted to the hospital with the diagnosis of Status asthmaticus and severe bronchitis.

When the child was first seen he had inspiratory and expiratory stridor with a prolonged expirium. His skin was pale gray and mottled, with lip and nail cyanosis. Proximal to his thumb knuckles on both hands we found reddened areas which were indurated. Otherwise he had scratch marks and some papillae which weren't exudative in character. He has a barrel-shaped thorax with horizontally placed ribs. The examination of the heart was not possible because of the Status asthmaticus: heart sounds were inaudible and the borders couldn't be found and the cardiac impulse couldn't be felt. His pulse was rapid and regular. The nostrils dilated with inspiration. A hyperresonant percussion tone was attained over both lungs. The breathing was vesicular in character, consisted almost entirely of whistling with an enormously prolonged expirium. Basally, the right lung had more muscial râles than the left. The abdomen was rigid and the liver was palpable one finger below

the rib margin. By fluoroscopy the lung fields showed an increase in transparency; ribs were horizontal and the intercostal spaces were wide. The diaphragma was deep and the excursions were very small. The hili were large and thick.

Therapy upon admission was:

Asthma mixture	4 x 5 ccm.
Penicillin	4 x 150,000 units
Streptomycin	2 x 200 mg.
Sympatol & Coramin	4 x alternating
Vi-Nicotyl	4 x 1 ampule I.M.

On the first day after admission the cyanosis had disappeared and no whistling was noted. The other râles were unchanged as was the prolonged expirium. On the third day he received an additional 4 x 200,000 units penicillin and 2 x 100 mg. Streptomycin. On the fifth day he still had the wet râles but there weren't any asthmatic attacks. On the eighth day the only signs of asthma were on auscultation. On the ninth day Vi-Nicotyl I.M. was stopped and he was given Redoxon and Vi-Nicotyl 3 x 1 tablet. On the twelfth day there weren't any râles and the expirium was still a little prolonged. The blood picture was normal after having shown an eosinophilia of 13 % on admission. On the twentieth day he was discharged as greatly improved.

SUMMARY

Bronchial asthma is a paroxysmal disease with respiratory distress caused by a sensitivity (allergy) to foreign proteins, either an inhalant or a food. There appears to be a positive connection between asthma and other allergic conditions such as exzema, urticaria and hives. Heredity plays an important role.

The chief causes of asthmatic dyspnea are three in number:

1. Spasmatic contraction of bronchiolar musculature
2. Swelling of bronchiolar mucosa
3. Increased tonus of the inspiratory musculature, escpecially the diaphragma.

Many investigators, chiefly Dainow and Halpern have shown both clinically and experimentally that nicotine amide, is a good antihistaminic.

CONCLUSION

Nicotine amide has been shown to posses good antihistaminic properties both in clinical and experimental trials. Because of this, it certainly is a good medicament for a physician to use in the treatment of allergic conditions. In the Jennerspital of the University of Bern, N.A. has been used as supporting treatment for bronchial asthma with success and may be recommended, especially during the beginning of the asthmatic paroxysm.

It is doubtful, however, whether it should be used alone, but it certainly should be used in conjunction with other drugs which are effective in treating specific sensitivity diseases, such as bronchial asthma, hay fever, eczema, urticaria, and hives.

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